

Treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis

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SUMMARY To test whether early treatment could postpone the chronic colonisation of the respiratory tract with mucoid strains of *Pseudomonas aeruginosa* in patients with cystic fibrosis, we performed a pilot study in 28 patients aged 2 to 18 years. A two week course of azlocillin (150 mg/kg/day) and tobramycin (10 to 15 mg/kg/day) was given after a mean duration of *P aeruginosa* colonisation of five months (range one to 11 months). Weight for height increased significantly by 3.5% (SEM 0.7%) of the predicted normal after chemotherapy. The eradication of *P aeruginosa* that was achieved in 18 children directly after hospital treatment was only temporary. Samples from only 10 and five patients remained negative three and six months after treatment, respectively. Five children remained free from *P aeruginosa* for a prolonged period of 14 to 32 months.

We conclude that, apart from the clinical improvement in all patients, some children might benefit from early antipseudomonas treatment with respect to the bacteriological outcome. Most children, however, experience only a temporary reduction in colonisation. Further investigations in form of controlled clinical trials seem justified.

Pulmonary infection is the primary cause of morbidity in patients with cystic fibrosis. *Pseudomonas aeruginosa* acts as the main bacterial pathogen that causes a persisting lung infection.¹ The *P aeruginosa* strains are usually of the mucoid, alginate producing variant, whose presence is usually a diagnostic feature of the disease.² The chronic colonisation with mucoid *P aeruginosa* is associated with an appreciable clinical deterioration of the patient. This poses a serious therapeutic problem as the eradication of mucoid *P aeruginosa* from sputum by antibacterial chemotherapy is virtually impossible.³

Several reports suggest that the appearance of mucoid *P aeruginosa* in patients with cystic fibrosis is preceded by an asymptomatic period of colonisation of the upper respiratory tract with non-mucoid *P aeruginosa* strains.⁴ A clinical trial with intravenous antipseudomonas treatment during the initial phase of *P aeruginosa* colonisation has not been reported.

Therefore we performed an open study to test the hypothesis as to whether early antipseudomonas treatment can eradicate *P aeruginosa* for a prolonged period of time, thereby postponing the

chronic stage of *P aeruginosa* colonisation in patients with cystic fibrosis.

Patients and methods

PATIENTS

All patients with cystic fibrosis attending the cystic fibrosis outpatient centre at the Hanover Medical School were regularly examined for *P aeruginosa* in the respiratory tract. The patients were included in the study according to the following criteria: (a) primary growth of *P aeruginosa* in the sputum or deep throat swabs, (b) demonstration of a second *P aeruginosa* positive specimen four to eight weeks after the initial positive sample, and (c) treatment at our centre for at least 12 months before the initial demonstration of *P aeruginosa*. Out of the 34 patients who met these criteria since June 1983, six children were excluded either because they were below 2 years of age (n=3), they had pulmonary surgery (n=1), or there were parental objections (n=2).

STUDY PROTOCOL

After the presence of *P aeruginosa* in sputum had

been confirmed in a sample taken several weeks after the initial positive specimen, the patients were asked to attend for treatment at the hospital at their earliest convenience. Patients and their parents gave informed consent.

The treatment was initiated on the day of admission. The combination of an initial azlocillin injection (150 mg/kg/day) followed by a tobramycin infusion (10 mg/kg/day) for 30 minutes was given at eight hour intervals. The routine treatment consisted of a high energy diet with a normal fat content supplemented with enteric coated, acid resistant pancreatic enzymes (Kreon or Panzytrat) and vitamins, including vitamin E. Additionally, physiotherapy and aerosol treatment with normal saline and salbutamol was continued throughout the hospital stay. Twelve patients received continuous oral antistaphylococcal antibiotics in addition to the treatment mentioned above.

LABORATORY AND CLINICAL INVESTIGATIONS

Before intravenous treatment venous blood samples were taken to determine the erythrocyte sedimentation rate, whole blood cell count, concentrations of immunoglobulins, serum creatinine, and urea, and the activities of liver enzymes. Trough and peak tobramycin serum concentrations were measured directly before and 30 minutes after terminating the sixth tobramycin infusion by using a fluorescence polarisation immunoassay (Abbott). The tobramycin dose was titrated to achieve peak serum concentrations between 6 and 12 mg/l.

Blood gases were analysed in arteriolar blood from the middle portion of the ear helix. Chest radiographs were taken if the last one had been performed more than six months ago. The condition of the chest was scored according to the classification of Chrispin and Norman⁵ by a radiologist who had no clinical knowledge of the patient.

Lung function was measured in 16 children who were older than 6 years. A body plethysmograph (Fenyves and Gut) was used for the determination of the residual volume and airway resistance. Areas of air trappings were evaluated by the helium dilution technique and calculated as follows: $(TGV-FRC)/TGV \times 100$ (TGV: thoracic gas volume, FRC: functional residual capacity). To interpret the lung function results a comparison with the normal values obtained in our laboratory was made.⁶ Results from uncooperative children without prior experience in lung function tests were excluded.

BACTERIOLOGICAL EVALUATION

Specimens obtained from deep throat swabs or sputa were plated on selective media. Appropriate

culture techniques were used to enhance the recovery of *P. aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus*. The standard disc technique was used to test the susceptibility of the infective organisms to antibiotics. Secondary cultures of the *P. aeruginosa* strains were either maintained on non-aerated agar slants at room temperature or stored at -70°C until use. Serotyping of *P. aeruginosa* strains was done by agglutination tests with commercial antisera (Pasteur Diagnostika).⁷ The phage typing pattern was assessed with the routine set of 20 bacteriophages.⁸ Pyocin typing was carried out by the spotting method.⁹ Strains were classified as different if they differed by serotype, and/or by at least one response to a pyocin indicator strain, and/or at least two responses to phages. Analyses were performed on *P. aeruginosa* strains obtained before the children were admitted to hospital, on the day of hospital admission, and during the six months after the throat swab had again become positive.

Results

Twenty eight children and adolescents with cystic fibrosis participated in the study. When admitted to the hospital the mean age was 9.0 years (range 2 to 18 years), whereas the mean age at initial *P. aeruginosa* colonisation was 8.6 years.

PRELIMINARY CLINICAL FINDINGS

The clinical state of the patients at the beginning of treatment is listed in table 1. Most children showed a mild to moderate degree of the disease, in which the mean values for weight, lung function tests, and oxygen pressure were in the normal range or slightly lower. Although most patients were clinically

Table 1 Clinical data and lung function test results of patients at the beginning of antipseudomonal chemotherapy

| | No of children | Mean | Range |
|------------------------------------|----------------|-------|-----------|
| Age (years) | 28 | 9.0 | 2-18 |
| Weight for height* | 28 | 93.7 | 71-136 |
| Chrispin-Norman score† | 19 | 8.8 | 2-23 |
| Oxygen pressure (kPa) | 22 | 10.5 | 5.1-13.1 |
| IgG (g/l) | 17 | 12.5 | 5-23 |
| Vital capacity* | 10 | 88.4 | 49-131 |
| Functional residual capacity* | 12 | 132.7 | 92-181 |
| Functional residual capacity/total | 10 | 0.541 | 0.42-0.74 |
| Trapped gas† | 13 | 32.4 | 16-53 |
| Airway resistance* | 13 | 115.9 | 31-288 |

*% Of normal predicted; † $(TGV-FRC)/TGV \times 100$; FRC=functional residual capacity, TGV=thoracic gas volume.

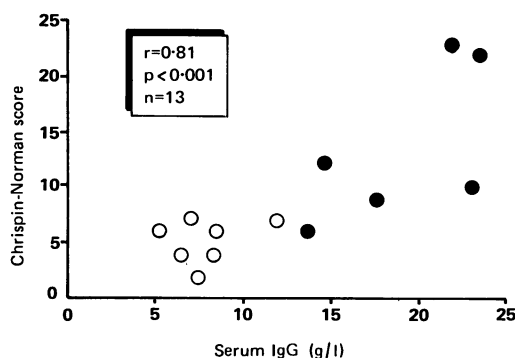


Fig 1 Association between serum IgG concentrations and Chrispin-Norman scores at the beginning of treatment. The patients were grouped according to the subsequent type of *P aeruginosa* colonisation: ○ denotes intermittent, ● chronic.

asymptomatic, three children had already experienced considerable pulmonary deterioration before the acquisition of *P aeruginosa*.

A linear correlation between IgG concentrations and lung involvement, expressed as the Chrispin-Norman score, was found ($r=0.81$, $p<0.001$ in 13 children) (fig 1).

BACTERIOLOGICAL FINDINGS BEFORE TREATMENT

The association of the onset of pseudomonas colonisation to treatment is shown in fig 2. Fourteen and 20 children were infected for the first time during the preceding four and six months, respectively. Most patients harboured rough *P aeruginosa*

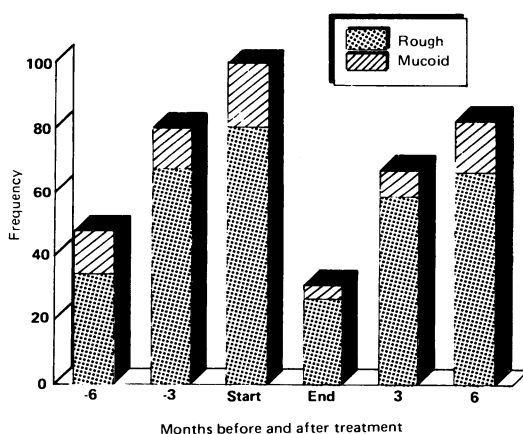


Fig 2 Frequency of *P aeruginosa* (rough or mucoid) in throat swabs or sputa before and after antimicrobial treatment.

strains, but in eight patients mucoid *P aeruginosa* strains were isolated at the time of admission, and in two patients mucoid variants had already been present in the initial positive specimen.

Additional bacteria were isolated in 21 of the 28 patients at the beginning of the antipseudomonas treatment (table 2).

S aureus was the most frequent pathogen, followed by *Enterobacter cloacae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumonia*, and *H influenzae*. Out of the seven patients who did not harbour any other pathogens besides *P aeruginosa*, five were on continuous oral antibiotics. Only seven of the 21 patients with multiple bacterial isolations had received such treatment.

CLINICAL RESULTS

Chemotherapy led to a significant increase in mean (SEM) body weight of 1.7 (0.3) kg after two weeks of hospital treatment. Percentage ideal weight for height increased from an initial mean (SD) 93.7 (12.4) to 97.2 (13.4) after treatment (mean (SEM) difference: 3.5 (0.7)% of ideal body weight, $p<0.001$). The corresponding SD scores were -0.61 before and -0.34 after treatment, respectively. The weight gain persisted for six months after the termination of treatment (fig 3). No significant improvements in lung function tests were found in the 10 children repeatedly tested. This may be due to the lack of severe abnormalities at the initiation of treatment. Indices of inflammation, which had been normal in most patients at the beginning of treatment, remained unchanged after antipseudomonas treatment.

SIDE EFFECTS

In general the treatment was well tolerated. All children received the complete two week course of

Table 2 Results of bacteriological examination of throat swabs or sputum taken before and after a two week course of antipseudomonal chemotherapy. Results are No of patients

| | Before chemotherapy | After chemotherapy |
|-----------------------------------|---------------------|--------------------|
| <i>P aeruginosa</i> (all strains) | 28 | 10 |
| Mucoid <i>P aeruginosa</i> | 8 | 1 |
| <i>Staphylococcus aureus</i> | 7 | 1 |
| <i>Enterobacter cloacae</i> | 4 | 0 |
| <i>Escherichia coli</i> | 2 | 2 |
| <i>Haemophilus influenzae</i> | 1 | 1 |
| Others | 4 | 1 |
| Two or more different bacteria | 3 | 0 |
| <i>Candida albicans</i> | 6 | 16 |

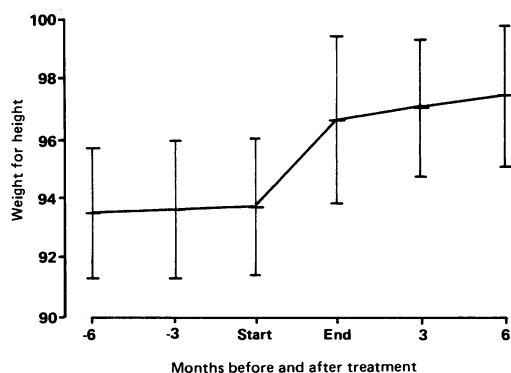


Fig 3 Weight for height expressed as the percentage of the predicted normal before and after antipseudomonal treatment. Results are mean (SEM).

Table 3 Total hospital admissions including the initial course of antimicrobial chemotherapy

| No of intravenous courses | No of children | <i>P. aeruginosa</i> colonisation | | Aerosol treatment |
|---------------------------|----------------|-----------------------------------|---------|-------------------|
| | | Intermittent | Chronic | |
| 1 | 14 | 7 | 6* | — |
| 2 | 7 | 3 | 4 | 3 |
| 3 | 5 | — | 5 | 5 |
| 4 | 2 | — | 2 | 1 |

The patients were classified according to the bacteriological results from throat swabs and sputa during the follow up period. Intermittent colonisation was defined as having less than 50% *P. aeruginosa* positive specimens. The five children who were free of *P. aeruginosa* for a prolonged period were included in this group. Chronic colonisation was defined as having more than 50% *P. aeruginosa* positive specimens.

*One patient was excluded from this analysis because of only an eight month follow up.

antimicrobials. Side effects were seen infrequently. Nevertheless, four children developed a skin rash after 10 days of treatment, with concomitant fever in two patients. After drug discontinuation, rash and fever subsided. No signs of drug induced nephrotoxicity or ototoxicity were found after treatment. Serum creatinine values did not increase compared with baseline values (57.6 $\mu\text{mol/l}$ before compared with 55.6 $\mu\text{mol/l}$ after treatment), and hearing tests gave no abnormal results.

BACTERIOLOGICAL RESULTS

Eighteen children were free of *P. aeruginosa* two days after treatment, and other bacteria were found in only five patients. Azlocillin resistance developed in two patients after treatment. *Candida* species were isolated from samples of 16 patients after treatment, however, compared with only six before (table 2).

The eradication of *P. aeruginosa* that was achieved in 18 patients directly after hospital treatment was only temporary. Three and six months after treatment, samples from only 10 and five children, respectively, remained negative. Recolonisation with *P. aeruginosa* was observed in four of the five patients after a lag period of 14, 20, 24, and 32 months after treatment. The patient with persistently negative sputa has been observed for 15 months after treatment until the present.

LONG TERM FOLLOW UP

The overall outcome of the 28 children including the last visit to the clinic is shown in table 3. Fourteen children needed additional antipseudomonas treatment due to pulmonary exacerbations, inadequate weight gain or weight loss, decline of pulmonary

function, or persistent signs of inflammation. Five of the 14 children received two additional treatments, and two children three additional treatment courses. This resulted in a total of 37 courses of intravenous antimicrobial treatment during a total of 370 months of follow up time—that is, 1.2 treatments per patient per year.

A group of nine patients received aminoglycoside inhalation treatment that consisted of 80 mg tobramycin twice daily after physiotherapy during the follow up period, usually starting after the second course of intravenous chemotherapy.

P. AERUGINOSA TYPING

Before the children were admitted to hospital a total of 57 different *P. aeruginosa* strains were isolated, indicating that most patients harboured two or more different *P. aeruginosa* strains in their respiratory tract. This was in contrast with the first positive throat swab after chemotherapy that showed only one *P. aeruginosa* strain in most cases. Serotyping, phagetyping, and pyocintyping showed that 17 patients had acquired novel strains, eight patients were harbouring the same set of strains as before antipseudomonal treatment, and two patients were infected with a mixed population of old and new strains.

RISK FACTORS FOR CHRONIC *P. AERUGINOSA* COLONISATION

In an attempt to define the risk factors of chronic *P. aeruginosa* colonisation, the patients were divided into two groups according to the incidence of *P. aeruginosa* positive throat swabs obtained at clinic visits during the years after initial antipseudomonas treatment.

Table 4 Mean clinical and laboratory data at the time of hospital admission classified according to *P aeruginosa* colonisation

| | <i>P aeruginosa</i> colonisation | | <i>p</i> Value |
|--|----------------------------------|----------------------------|----------------|
| | Intermittent (<i>n</i> =10) | Chronic (<i>n</i> =17) | |
| Age (years) | 8.2 | 9.8 | 0.370 |
| Duration of colonisation (months) | 4.9 | 5.2 | 0.717 |
| Weight for height (%) | 96.7 | 93.3 | 0.561 |
| Vital capacity (%) | 79.3 | 94.5 | 0.304 |
| Functional residual capacity/total lung capacity | 0.548 | 0.537 | 0.856 |
| Oxygen pressure (kPa) | 11.3 | 10.0 | 0.09 |
| Chrispin-Norman score | 5.1 | 11.5 | 0.01 |
| IgG (g/l) | 8.2 | 16.4 | 0.002 |
| Serum urea (mmol/l) | 5.2 | 3.7 | 0.024 |

For definition of the colonisation groups refer to table 3.

Table 5 Frequencies of pathogens other than *P aeruginosa* in a total of 204 throat swabs or sputa obtained at clinic visits during the two years before hospital admission grouped by outcome of *P aeruginosa* colonisation. Results are No of specimens (% of each group)

| Time before treatment (months) | Pathogens not found | Gram positive bacteria | Gram negative bacteria | Yeasts |
|-----------------------------------|---------------------|------------------------|------------------------|--------|
| 24-12 | | | | |
| <i>P aeruginosa</i> colonisation: | | | | |
| { Intermittent (<i>n</i> =34) | 19 (56) | 3 (9) | 10 (30) | 2 (6) |
| { Chronic (<i>n</i> =65) | 40 (61) | 6 (9) | 11 (18) | 8 (12) |
| 12-1 | | | | |
| <i>P aeruginosa</i> colonisation: | | | | |
| { Intermittent (<i>n</i> =38) | 18 (47) | 6 (17) | 7 (18) | 7 (18) |
| { Chronic (<i>n</i> =67) | 27 (40) | 9 (14) | 23 (34) | 8 (12) |

Table 4 compares clinical and laboratory results obtained at the beginning of the first intravenous treatment of the two groups of patients. Children who subsequently developed intermittent colonisations were observed compared with patients with chronic *P aeruginosa* colonisations. Surprisingly, there were no differences in age or in duration of *P aeruginosa* colonisation before treatment, nor in weight for height or lung function. However, the chest radiograph was significantly worse in the group which later became chronically infected. In addition, high initial serum IgG concentrations and low serum urea concentrations were associated with chronic *P aeruginosa* colonisation.

Table 5 shows the incidence of bacteria apart from *P aeruginosa* during a period of two years before the children were admitted to hospital. During the first period (24 to 12 months before treatment) no throat swab yielded *P aeruginosa*, but other Gram negative species were isolated in 21 and Gram positive bacteria in nine of 99 specimens. The frequency of

bacterial isolations increased to 43% during the year before treatment. The frequency of additional bacteria before antipseudomonas treatment did not differ in the two patient groups.

Discussion

In the present study intravenous antipseudomonal treatment was given early with respect to the current treatment schedules for *P aeruginosa* colonisation as an attempt to eliminate the bacteria from the respiratory tract, thereby trying to postpone the chronic phase of *P aeruginosa* colonisation. The results, however, show that the permanent eradication of *P aeruginosa* from sputum is very difficult to achieve in most patients, even if only a few months have elapsed since the first detection of *P aeruginosa*. Although bacterial typing indicates that the initial *P aeruginosa* strain can be successfully eliminated by antimicrobial treatment, other *P aeruginosa* strains will subsequently take residence in the respiratory

tract, because the compromised host with cystic fibrosis remains susceptible to recolonisation with *P aeruginosa*.

Raised serum IgG concentrations as well as the severity of chest involvement, measured by the Chrispin-Norman radiological score, were identified as risk factors for chronic *P aeruginosa* colonisation. This suggests that host factors play an important role in the progression of colonisation.

In patients without cystic fibrosis, pseudomonas colonisation is seen only after injury to the respiratory mucosa has occurred—for example, during endotracheal intubation or in patients with tracheostomy or chronic bronchiectases. The initial step of bacterial colonisation is the adherence of the organism to the cells of the mucosal surface.¹⁰ Woods *et al* identified the loss of fibronectin from cell surfaces as a promoting factor for the initial epithelial damage in cystic fibrosis.¹¹ Investigations performed in our department with buccal cells from patients with cystic fibrosis showed that *P aeruginosa* can attach more easily to cells from chronically infected patients with cystic fibrosis than to cells obtained from these patients without bacterial colonisation.¹² In addition, there was a positive correlation between the duration of *P aeruginosa* colonisation and the adherence of *P aeruginosa* strains to buccal epithelial cells.

The fact that 60% of our patients grew Gram positive or Gram negative bacteria in addition to *P aeruginosa* in the year before initiation of treatment indicates that *P aeruginosa* is only one of several different bacterial species invading the respiratory tract. On the other hand, this finding could also mean that the mucosal damage caused by certain bacteria contributes to the subsequent binding of *P aeruginosa*.

After bacteria have successfully adhered to the mucosa or mucins of the respiratory tract the organisms start to replicate, release toxins, and finally, induce mucosal damage. In the current study, patients who later become chronically infected with *P aeruginosa* showed a more severe degree of lung involvement on initial chest radiographs compared with patients with only intermittent colonisations. If it is assumed that higher radiological scores are caused at least in part by defective endobronchial clearance mechanisms, these results show that the importance of impaired mucociliary clearance for the persistent growth of *P aeruginosa* should not be underestimated.

The bacteriological results obtained from the current study were in agreement with those reported by other authors.¹³ Two thirds of the patients were free of *P aeruginosa* after a two weeks course of antipseudomonas treatment. An encouraging find-

ing was the absence of *P aeruginosa* in the respiratory tract of five children over prolonged periods of 14 to 32 months. Whether this is due to antimicrobial treatment or rather to specific host factors remains unclear, as no control group was investigated in the present study.

The clinical benefit of the treatment was shown by a significant increase in weight for height, which persisted during the six months after chemotherapy. It must be emphasised, however, that antibiotics eliminated other Gram negative and Gram positive bacteria in addition to *P aeruginosa*. The weight gain may therefore not only be attributed to the decrease of *P aeruginosa* colonisation, but to a more generalised antimicrobial action. Furthermore, hospital treatment in itself may improve symptoms and well being in cystic fibrosis patients.^{14 15} This could be because the whole treatment programme, including physiotherapy, can be performed on a regular basis, which is not always possible at home.

If recolonisation with *P aeruginosa* occurs after antimicrobial treatment, the question arises whether or not repeated courses of antimicrobials should be given at regular intervals, as proposed by Szaff *et al*.¹³ The Danish group reported stable pulmonary function data during the first five years of colonisation with *P aeruginosa*, if the patients were treated every three to four months, whereas a historical control group showed a decline in peak expiratory flow during the same period. The major drawbacks of this kind of treatment are the interference with the patients' social life and the high costs of treatment. Inhalation of aerosolised antibiotics for months and years on an ambulatory basis has been proposed as an alternative approach for adult patients with cystic fibrosis and chronic *P aeruginosa* colonisation.¹⁶ No data are available concerning the optimal onset of aerosol treatment, however, and the question as to which patients will benefit most has not been resolved.

In conclusion, from the results of the present pilot study early treatment of *P aeruginosa* colonisation appears to be a reasonable approach in patients with cystic fibrosis. A temporary reduction in colonisation can be achieved in most children. As the patients remain susceptible to recolonisation, however, only few patients will benefit from an improved prognosis due to a prolonged *P aeruginosa* free interval. Prospective randomised studies are needed to investigate the value of early antibiotic treatment in patients with newly detected *P aeruginosa* colonisation. Moreover, the role of host factors for the development of chronic *P aeruginosa* colonisation should be studied in more detail.

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